MELANOTIC TUMORS*

NONMELANOTIC MELANO-EPITHELIOMAS AND THEIR RELATION TO THE MELANO-EPITHELIOMAS

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From a morphologic standpoint there are three main contentions relative to the origin of melanotic tumors:

1. They arise from the epidermis.
2. They are of mesodermal origin.
3. They are specially characterized cells of mesodermal origin, so-called chromatophores.

Ewing's noncommittal view is tersely expressed: "Theoretical considerations favor the origin of all melanomas from the mesoblastic chromatophore, while histology favors their origin from epithelial cells which have taken on pigmentary function."

More recently investigators have attempted to settle the controversy by study of the embryology, but again, they too differ in their conclusions. Acton in his embryologic studies on the tree frog concludes that in lower animals the melanoblasts form a large continuous sheet under the skin surface layer (primitive pigment sheet) which is closely related to the angioblasts of the cutaneous respiratory capillaries.

Acton believes that the melanoblasts (which form pigment) are primarily in the dermis, and that processes from these cells envelop the basal cells of the rete malpighii, and the pigment diffuses between the cells into the intercellular bridges. He finally concludes that there are two types of cells involved in the melanotic tumors: (1) melanoblasts, giving rise to melanosarcoma, and (2) angioblasts (which with the melanoblasts form the benign moles) giving rise to malignant endotheliomas.

Spencer is a strong protagonist of the epidermal origin of the melanotic tumors. His observations on the ink-sac of the sepia show that epithelial cells form melanin pigment. He further observed that in embryo frogs branched pigmented cells develop in the epidermis and pass downward into the subepithelial tissues. This is in direct contradiction to Acton's observations.

Spencer, in his studies on the eye, states that the pigment of the choroid is developed from the retina either by the ingestion of pigment by the cells of the choroid acting as phagocytes, or the cells have grown down into the choroid from the retina. He explains the distribution of melanin-pigmented

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cells in the body by the fact that primarily they developed around the neural tube for protection of the central nervous system. As further development occurred, the pigmented cells first spread into the epidermis and then deeper into the mesoblast of the immediate neighborhood and were then carried along the parietal and visceral layers of the mesoblast along with the outgrowing nerves, especially the sympathetic nerves. Pigment cells, therefore, are present in the epidermis, in the rete malpighii and to a less extent in those of the rete spinosum and the corresponding epithelial cells which produce shafts of hair. While in the dermis, the pigmented cells may occur singly, in patches, or in sheets at varying distances from the epidermis, but they all originate as dendritic cells which have penetrated from the epidermis downward into the dermis either as melanophores (cells that are pigmented) or as melanoblasts (colorless cells) that become pigmented in the dermis. The epidermal cells make the pigment while the mesoblastic cells take up the pigment freed by the breaking down of epithelial cells, as phagocytes.

Smith states that there are two types of melanotic tumors: those arising from the skin, hair follicles, retina, and certain regions of the brain are epithelial in origin while those from the iris and choroid and the "mongolian spot" (pigment spot found over the sacrum in the dark races) are mesothelial in origin.

Dawson gives an admirable review of the various theories of origin of the melanomas, and from his studies concludes that melanotic tumors are epithelial in origin. But he agrees with Broders and MacCarty that it is not necessary to accept Unna's view that nevi are epithelial cells snared off in early embryonal life. He believes rather that the difference in morphology should be regarded as an expression of their capacity for differentiation. Therefore, the changes in the epidermis are the different stages of a process "uniform in its initiation but manifold in its development"; hence the reason for their mimicking the picture of carcinoma, sarcoma or endothelioma. In this view he refers to Marchand and Adami who pointed out the relationship between the "differentiation and both the proliferative and functioning capacities of cells." He maintains that a great many observers are misled by the fact that both epidermal and mesodermal cells may show pigment. But the epidermal cell is the creator of that pigment and the mesodermal cell is only a phagocyte carrying pigment.

Dawson takes issue with Acton's idea about his "primitive vascular pigment sheet" in the tree frog being mesoblastic in origin, because it represents a more mature stage of pigment formation. He cites Kornfeld who found melanoblasts (in the larval stage) in the epidermis. To regard the primitive pigment sheet in the subepidermal tissues in the mature position of mesoblastic origin "disregards the phases of their migration which are coincident with the phases of metamorphosis of the larval amphibian."

Relative to the choroidal tumors which have been cited as a good reason for believing them to be of mesoblastic origin because the choroid is mesoblastic embryologically, he repeats Spencer's observations as well as his own;

namely, that the retinal pigment cells migrate to the choroid and provide the choroid with pigment. He concludes that malignant melanomas arise from carcinomatous changes in actual nevus cells derived from the epidermis and embedded in the dermis, or from a genetic process starting in the epidermis and progressively undergoing morphologic changes as they migrate into the dermis. He summarizes his ideas as to the many differences in morphology as follows: "These varied series of epithelial cell transformations, resulting in tumors of such diverse types, allow of only one interpretation, that of their epidermal origin and an evidence of the amazing power of anaplasia and redifferentiation of the epidermal cell." This is in accord with the earlier statement of Broders and MacCarty that malignant melanotic tumors are due to the "migratory hyperplasia of the basal (regenerative or germinative) layer of the skin and invades the subcutaneous tissues and distant organs."

Metastasis of Melanotic Tumors.—One of the arguments in favor of the epithelial origin of the melanotic tumors is that they metastasize by way of the lymph-channels to the nearest lymph-nodes. But those favoring the mesothelial origin cite the extension of ocular melanomas by way of the blood stream. As a matter of fact both methods of metastasis occur, but more often the lymphatics are involved. It is only when the tumor has grown rapidly that the blood stream is invaded. Miescher applied the dopa reaction to a metastatic growth from melano-epithelioma with positive results, showing that also the metastatic tumor cells are ectodermal in origin.

Acton, who believes in the dual origin of melanotic tumors, asserts that the "melanosarcomas" spread by rapidly eroding blood-vessels while the melano-endotheliomas spread by permeation along the lymphatics.

Cairns describes a primary tumor of the eye with metastasis to the scapula after eighteen years. He says that melanotic tumors frequently reproduce in bone.

Metastasis may occur in any organ, including the heart muscle and the spleen. Tumors of the eye often metastasize to the liver.

Melanin.—In order to understand fully why some tumors of the melanotic type are pigmented and some are not, it would be well to review our knowledge of melanin. Melanin is a term given to "a varied and complex group of pigments which give color to hair, skin and eyes in man, and are responsible for the color of animals, birds and insects." [30]

Physical and chemical properties.—Ewing states that melanin consists of carbon, hydrogen and nitrogen in the ratio of 1:5:5 and varying amounts of sulphur. Acton says that from 8 to 13 per cent. of sulphur is present while Spencer gives sulphur a content of from 5 to 12 per cent. Melanin contains no iron. Heated in strong alkali melanin from melanotic tumors yields indol, skatol, and volatile fatty acids and ether-soluble acid giving a dark blue color with ferric chloride. The chief product is melanic acid. Under dry heat melanin gives off pyrrhol.

Origin.—The theories as to the origin of melanin are at wide variance. Some authors claim that melanin originates from the hæmoglobin of the blood.

But melanin does not contain iron unless there has been an extravasation of blood into the tumor. Meirowsky, Rossle and Staffel (according to Acton) believe that the origin of melanin is from nucleolar matter of melanoblasts. The coincidence of increased melanin and nuclear degeneration is taken by them to be a distinct sign of a causal relationship between the two. Lubarsch believes that the high sulphur content of melanin is an indication of the pigment being connected with decomposition of albumin. But Acton refutes the nuclear degeneration theory by the fact that the most virile cells have the most pigment. Spencer believes that the nuclear degeneration is a pressure-effect of the pigment in the cells.

Many substances have been said to be the mother-substance of melanin; namely, tyrosin (Gessard, Dunham), epinephrin (Jäger, Neuberg, Meirowsky, and others) and tryptophane (Spiegler, Eppinger, Fasal, and others).[8]

Until recently the general belief was that melanin pigment was produced by the action of an oxidase (tyrosinase) found in the epidermal cells, on an oxidizable colorless chromogen (melanogen) which is formed by the metabolic activity of the cell from the protein molecule brought to it. The term "melanogen" originated with Thormählen who found that the urine of patients suffering from melanotic carcinoma darkened on standing.[32] Tyrosinase is so called because of its action on tyrosin and other aromatic bodies containing an hydroxyl group to form melanin bodies. Tyrosinase has been found widely distributed in the tissues. Gessard[30] found it in melanotic tumors of the horse. Artificial melanin has been formed by the action of tyrosinase of Lepidopteran larvæ on tyrosin.

Recently Bloch[6] brought out the dopa reaction by treating fresh skin or frozen sections with a 0.1 or 0.2 per cent. watery solution of 3–4 dioxyphenylalanine for twenty-four hours at room temperature, or 37° C. A positive dopa reaction is due to oxidation (with condensation) of the dioxyphenylalanine into a dark (smoky-gray, dark-brown or very black) pigment, the dopa melanin which may be diffuse or in granules. The site of the positive dopa reaction is restricted to the protoplasm (not the nucleus) of the malpighian cells of the basal cell layer (and in stronger reactions also the prickle-cell layer) the infundibulum of the hair follicle (Follikel trichter) and the cells of the outer root sheath and hair matrix. In other words, the dopa reaction is restricted to cells of ectodermal origin.[9] The positive dopa reaction should be distinguished from a pseudo-reaction which is found in the leucocytes and sweat gland cells of the cutis (mesodermal origin) which is due to oxidation of dopa by phenolase or polyphenoloxydase present in these cells. The form of cell which gives a positive dopa reaction may be the normal epidermal cell or, in stronger reactions, a dendritic type of cell with long branching protoplasmic processes which enmeshes the neighboring cells. The intensity of the dopa reaction is proportional to the strength of the dopa-oxydase present in the cells. This varies not alone according to species of animal or race, but also from cell to cell in the same section. Some of the cells may be darkly pigmented, others only slightly, and still others not at all. Thus it is easy to understand that under pathologic conditions the variations may be even more striking; this is well shown in the skin and hair of the albinos and vitiligo spots where the dopa reaction is absolutely negative because dopa-oxydase is lacking in these cells.[7, 19] This is also true in the white hair-spots in animals. The intensity of the reaction may also be changed by physical, chemical and infectious influences. The reaction is more intensive after exposure to sunlight, Röntgen-rays, thorium-x, quartz lamp, and so forth[22]; it is most intensive in the pigmented nevus and is absent in vitiligo spots.

Bloch [8] went further to prove that this dopa-oxydase is a ferment, that it is an oxidizing ferment, and lastly that it is a highly specific ferment. This intracellular enzyme is labile and its thermolability varies with the individual and the type of animal. At from 57 to 80° it is weakened and at 100° its ferment action is disturbed. It is destroyed by drying, imbedding in paraffin, ammonium sulphate, dilute ethyl alcohol, acids, alkalis (except in very dilute solutions), proteolytic ferments, strong oxidizing or reducing agents, poisons (such as hydrocyanic acid), ether, chloroform and benzol. Röntgen-rays and ultraviolet rays have very little effect. Distilled water and physiologic sodium chloride solution have a detrimental effect after a time.

To prove that dopa-oxydase is specific for 3–4 dioxyphenylalanine Bloch attempted to obtain a positive dopa reaction by using other chemical agents allied to dopa. These substances were divided into two groups, those without and those with a pyrocatechol nucleus Among the many substances without a pyrocatechol nucleus were tyrosin, hydroquinol, homogentisic acid, tryptophane and others. Among those with a pyrocatechol nucleus were pyrocatechol itself and many substances which were assumed to be intermediate to dopa. All these substances gave a negative dopa reaction and warranted the following conclusions about the substance acted on by dopa-oxydase. (Fig. 1.)

1. It must be a pyrocatechol derivative.

2. Both hydroxyl groups in the dopa must be intact, since substitution by a methoxy group gave a negative dopa reaction.

3. The side-chain must have at least a propionic acid group and an amino group.

This showed that 3–4 dioxyphenylalanine (or a closely allied substance) is closely related to, or actually is the substance acted on by dopa-oxydase to form dopa-melanin, an insoluble pigment. The dioxyphenylalanine employed was either a levorotatory or racemic (synthetic) form and little difference was noted in these experiments except perhaps in the very light reactions it was noted that the levorotatory form gave a stronger reaction.

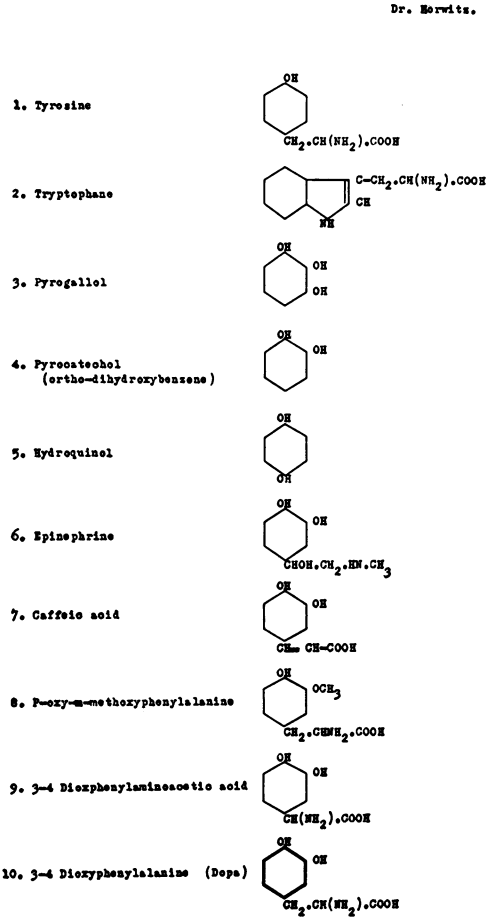

FIG. 1.—Chemical formula.

Fate of melanin.—The fate of melanin in the body has been variously described. Some claim that the pigment enters the blood and is excreted by the glomeruli of the kidney as pigment granules. Others maintain that melanin is changed to colorless melanogen by the liver and then is excreted by the kidney.[26] Nepvin (quoted by Acton), claims that in malignant melanomas mela-

nin is found in the leucocytes in the blood producing melanemia, due to the great number of leucocytes carrying melanin. Acton believes that the achromatic melanogen excreted by the kidney is a reduction substance and not the mother substance of melanin.

Distribution of melanin.—Normally melanin is present mainly in the skin, eye and parts exposed to light.[14] It is also present to some extent in the central nervous system. In the skin it is found in the deeper layers of the rete malpighii and in the branching cells of the corium in the transition zone between the dermis and epidermis, and about the blood-vessels. In the dark races almost all the cells of the basal layer of the rete malpighii are pigmented but in the white races only the areola and mucocutaneous layer of the anogenital region are pigmented.[14] However, that the basal cells of the skin of the white races are potential melanin formers can be easily proved by the bronzing on exposure to the sun.[22] The fetus of both white and colored races have pigment in the basal cells of the rete malpighii, but the cells are depigmented in the white races. In the eye it is present in the cells of the choroid, iris, and ciliary process as phagocytosed pigment, and in the retina where it is a product of a neuro-epithelial cell.[14, 20] The other sites where melanin is present are the brain, cord and occasionally the internal organs. These are due to migration of melanin-producing cells along sympathetic nerves or vessels.

Function of melanin.—The function of melanin pigment is to protect against light, heat and moisture. In the animal it has the function of "adaptation, attraction and offensive and defensive mimicry.[13] Ewing quotes Eppinger who concludes that excess of pigment and its products, especially indol and skatol, are the cause of the overgrowth of cells. Artificial pigment or that extracted from tumors or urine are toxic for animals. Adler believes that the toxic effect may be due to the transformation of melanin into melanic acid which is the toxic agent.

Relation of Nonmelanotic Melano-epithelioma to Melano-epithelioma.—The absence of pigment in the melanotic tumors has been explained by Acton according to his conception of the two-cell theory, as follows: those arising from the melanoblasts, melanosarcoma type, naturally would have pigment while the malignant melano-endothelioma type arising from both angioblasts and melanoblasts would have both pigmented and nonpigmented areas. And since one or the other of the cells may predominate, there would be no pigment if only the angioblasts were present.

Hertzler and Gibson accept Ribbert's chromatophore theory. The melanotic tumors arise from chromatophores whose specific function is to form pigment. These cells, however, often lie dormant, are colorless and give rise to tumors which differ from melanotic tumors only in not containing pigment. They claim that the tumors which tend to ulcerate usually contain little pigment.

Ribbert explains the presence of pigmented and nonpigmented cells side by side in some tumors, as cells which have maturity and immaturity, respectively. The immature cells cannot produce pigment. The nonpigmented part of some tumors may be due, however, to depigmentation.

Thibaudeau and Schreiner in their study of twenty-seven cases of melanotic cancer

believe that there is no relation between the amount of pigment found in the tumor and the degree of malignancy.

Broders and MacCarty, in their review of seventy cases of melano-epithelioma, maintain that the nonmelanotic tumors belong to the same family as the melano-epitheliomas and differ only in the lack of pigment. They have the same cell appearance as the nonpigmented areas of melano-epitheliomas and it is reasonable to believe, these authors state, that if the cells of the nonmelanotic tumors were given the opportunity to differentiate far enough, they would produce melanin.

Broders [3] says that differentiation is a means that malignant tumors have "of putting on the brakes." Melanin production is a form of differentiation. Producing pigment is a function of certain epithelial cells and when the cells proliferate rapidly they follow Marchand and Adami's law,[14] that as a cell carries out its vegetative powers it sacrifices its functioning powers; and we would therefore expect the nonmelanotic melano-epitheliomas to be rapid in growth, and their cells to be more primitive in type.

Another factor that shows that nonmelanotic melano-epitheliomas belong to the same family as the melano-epitheliomas is the presence of melanuria, as reported by various observers in nonpigmented tumors.[23, 25] It must be assumed, therefore, that the chromogen is present but is not acted on by the oxidase either because the cell is too immature to have the oxidase, or if it does have oxidase, not enough opportunity is offered for the oxidase to act on the chromogen, owing to the rapidity of growth.

Pathology.—The tissues in forty-nine cases of nonmelanotic melano-epithelioma were studied microscopically. In certain cases it could be easily demonstrated that malignant changes began in the basal-cell layer of the rete malpighii, either in the papillary or the interpapillary portions of the epidermis. (Fig. 2.) The malignant cells, epithelioid in form, could be seen streaming from one portion of the epithelium into the cutis and then spread out in its upper part. However, in other cases the malignant cells were restricted to the cutis and the epithelial layer was intact. In still others malignant cells from the cutis could be seen invading the subepithelial part of the cutis and even breaking through into the epithelial layer. In only a few cases was lymphocytic infiltration present in the subepithelial layer of the cutis.

The arrangement of the malignant cells was varied. In some it assumed the picture of a fibrosarcoma. (Fig. 3.) The cells were elongated markedly and arranged in whorls. In others an alveolar arrangement was present. (Fig. 4.) In most cases, however, the malignant cells were in solid masses resembling a large or small round-cell sarcoma or massive carcinoma. Only occasionally were the cells arranged in columns or cords. In a few cases the papillary portion of the cutis could be seen invaded by epithelioid cells from the epidermis, and as these cells forced their way into the deeper layers of the cutis they assumed an alveolar arrangement in one area and resembled a fibrosarcoma in an adjacent area, while in still another area the cells appeared definitely carcinomatous. There was little or no intercellular stroma apparent as a rule. Melanin was absent, but blood pigment was present in one case in the form of large irregular patches of a bright sheen. In a few cases the cells were closely applied to young blood-vessels.

The forms of the individual cells were as varied as their arrangement, spin-

dle-formed, round and oval, or markedly elongated. In some they approached more nearly epithelial cells. The nuclei were large in proportion to the rest of the cell, vesicular and hyperchromatic. Some were "one-eyed" (Fig. 5) showing one darkly stained nucleolus but more often there were two or three nucleoli in a meshwork of chromatin. Some of the nuclei appeared stippled, and mitotic figures were more or less numerous. Occasionally vacuoles were

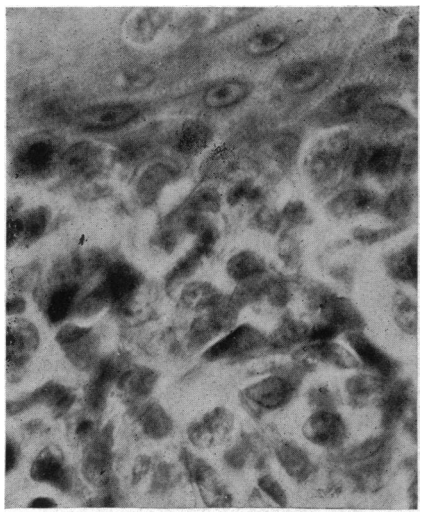

FIG. 2.—Nonmelanotic melano-epithelioma arising in the germinal layer of the skin. The cells are in direct continuity with the stratum germinativum.

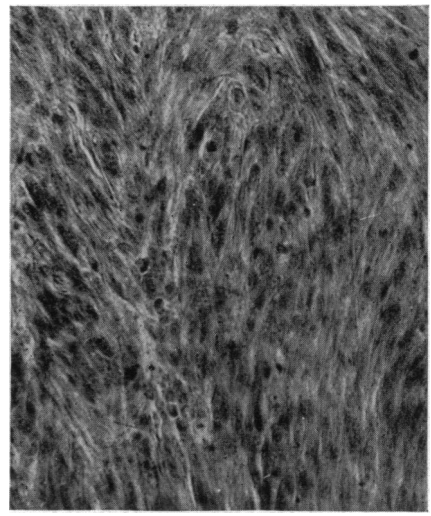

FIG. 3.—Elongated spindle cell simulating fibrosarcoma (x140).

seen in the nuclei. (Fig. 6.) A few sections were found replete with large giant cells with huge nuclei. According to Broders' gradation of epitheliomas all the tumors were graded 4, that is, there was little or no attempt at differentiation. The large cells apparently represent an embryonal state. In general every tumor studied gave the impression of a severe malignancy.

Whatever the form or arrangement of the cells, however, it was apparent that all the tumors were epithelial in origin. The variation in form was only evidence of a different stage of "dedifferentiation" or regression to a more embryonal state of development. This, with the absence of pigment, explains the highly malignant nature of the nonmelanotic melano-epitheliomas.

Clinical Considerations.—Malignant melanotic tumors were first described as occurring in horses in the latter part of the eighteenth century. Laennec first wrote about it in man. The nonmelanotic character of some of the tumors or nonpigmented areas in pigment tumors has been mentioned by many, but reports of cases that were nonmelanotic are few.

It is well known that the primary melanotic tumors may be pigmented and the secondary tumors nonpigmented or only partially pigmented. The reverse is also true.

Etiology.—The primary cause of melanotic tumors is as much a mystery as is the cause of other malignant tumors. Of the predisposing causes many

factors must be considered, namely, trauma, presence of a mole, wart or nevus, site of mole, age, and race.

The history of trauma is in many cases unreliable, but in some cases it is too definite to be ignored, especially when trauma is considered in its broader sense, including in its meaning such factors as chronic irritation, ill-advised and improper surgical procedures or the use of escharotics. In the cases reviewed

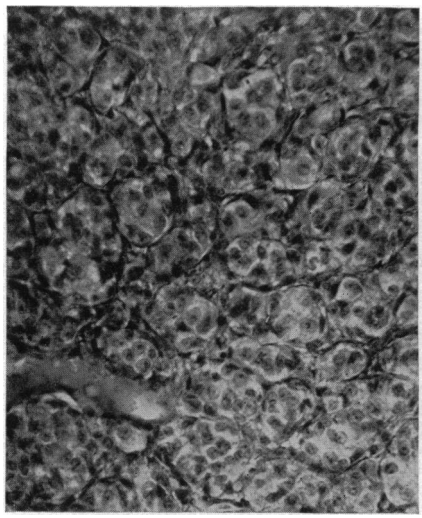

FIG. 4.—Alveolar arrangement of some of the cells (x140).

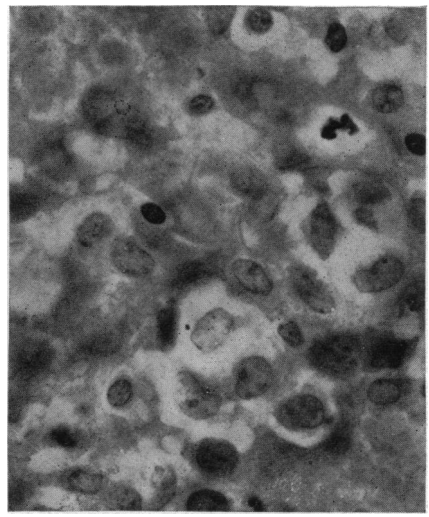

FIG. 5.—"One-eyed" cells and mitotic figures (x500).

here irritation was caused in many instances by improper shoes and in some the activity of the tumor was definitely accelerated after the use of escharotics, ligation, carbon-dioxide snow, and ill-advised operations. Activity seemed to begin in twenty-eight of the forty-nine cases (57.1 per cent.) following injury, irritation, or some means used for the removal of a mole or wart.

Heredity is probably not a factor. Pfingst and Graves report a case of melanosarcoma of the eye in two brothers. They thought it to be coincidental. It is interesting to note that it is considered hereditary in horses. Incidence of carcinoma in the family was found in only six of our cases, but this figure is probably too low. The tumors may occur at any age, but usually past middle life. In this series of forty-nine cases the average age was fifty and three-tenths years, the youngest patient being twenty years and the oldest seventy-seven.

AGE BY DECADES

Years	Patients	Years	Patients
20–29	5	50–59	12
30–39	.	60–69	16
40–49	7	70–79	2
			—
			49

Twenty-seven of the patients were males and twenty-two were females.

The dark races seem to be immune to this type of tumor. It is well known among veterinarians that gray horses after the age of ten become white due to loss of pigmentation in the hair, and then they are prone to melanotic carcinoma. Lubarsch quotes Folger's statistics of 527 carcinomas in 175,745 horses, 226 (42.88 per cent.) were melanotic in type. Of 2274 malignant tumors in 18,113 cadavers of human beings, twenty (0.89 per cent.) were melanotic. Although it is true that the dark races are less prone to malignancy in general, still it is worthy of note that the melanotic tumors are almost unheard of in the dark races in spite of the fact that melanomas are more common in them than in the white races.[32] Seligman noted among the natives of New Guinea that pigmented moles were common on all parts of the body but none had been seen to spread or give to tumor formation. Gilchrist,[32] Sutton and Mallia and Stevenson, Hazen, Carmichael, and Menage describe malignant melanoma in negroes. In my series all patients were white.

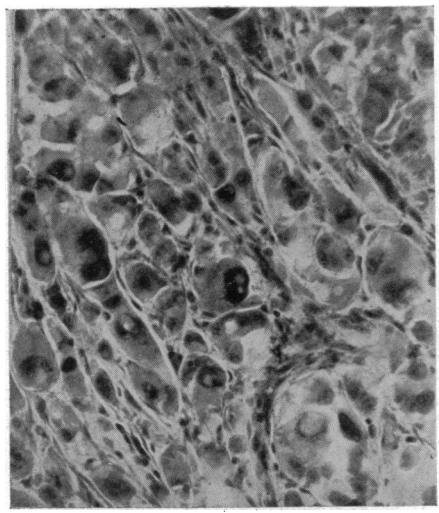

FIG. 6.—Enormous type of cell with large nuclei, some of which are vacuolated (x140).

In eighteen (36.7 per cent.) of the forty-nine cases of nonmelanotic melano-epithelioma the patients gave a history of the presence of a mole, wart, or nevus. In ninety-one cases of melanotic tumors reported by Coley and Hoguet there was a history of mole in thirty-six (39.6 per cent.). In 33 per cent. of Dawson's cases there was a history of mole. In Broders and MacCarty's series of seventy cases, a history of mole, wart or nevus was given thirty-five times (50 per cent.). Apparently the presence of a mole does not indicate whether or not the resulting tumor will be pigmented.

SITE OF THE PRIMARY TUMOR

Site	Cases	Site	Cases
Foot (including ankle)	17	Nose	1
Leg	7	Eye	1
Thigh	2	Ear	1
Groin	2	Cheek	4
Thumb	2	Neck	2
Arm	1	Chest	2
Axilla	3	Back	2
Forehead	1	Vagina	1
	49		49

It will be noted that of the twenty-eight cases (57.1 per cent.) in which the lesion was on the lower extremities, it was on the foot (the part covered by the shoe) in seventeen (34.7 per cent.). (Fig. 7.) In Coley and Hoguet's series of ninety-one cases the pigmented tumors were on the lower extremities (from groin to toes) in thirty (33 per cent.), and in seventeen (18.7 per cent.) of these, on the foot and ankle; irritation was noted in sixteen of these seventeen cases. In Broders and MacCarty's series of seventy cases of melano-epithelioma, the lesions were on the lower extremities in twenty-nine (41.4 per cent.), and of these, sixteen (22.8 per cent.) were on the foot and ankle. In Dawson's series of thirty-six cases of moles showing transition to malignancy, ten (27.7 per cent.) occurred on the lower extremities and seven (19.4 per cent.) were on the foot. In thirty-one cases in which there was metastasis, Dawson reported nine (29 per cent.) on the lower extremities and of these six (19.4 per cent.) were on the foot. Hertzler and Gibson state that amelanotic types on arm or scalp have not been established. In the series reported here one occurred on the arm of a woman, aged twenty-nine, with metastasis to the axilla. A mole had been present since birth. In one case there was a history of chronic ulcer on the temple.

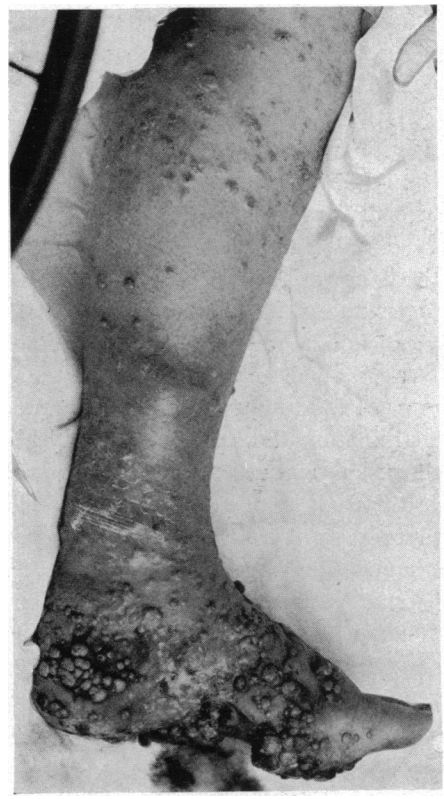

FIG. 7.—Nonmelanotic melano-epithelioma arising from an irritated spot on the heel, showing metastasis to skin of foot and leg.

Symptoms.—The symptoms in these cases are varied. There is usually a history of a mole or wart which may have been noticed since birth or for many years. This was either bruised, injured or irritated for a long time, especially if occurring on the foot. As was formerly stated, the history of injury is open to question in some of these cases, but on the other hand, in many others the history is too frank to be ignored. A discharging sore or bluish discoloration may follow an injury, or the mole or wart may gradually increase in size and then break down. The discharging sore may heal only to break down again in a short time. It is usually at this time that medical aid is sought and more often than not the true condition is unsuspected by both physician and patient. The area is either excised, or other means of removal such as curettement, ligation, carbon-dioxide snow or escharotics may have been used. This usually is quickly

followed by early recurrence locally and the activity of the tumor is manifested by rapid dissemination to the neighboring lymphatics. It is the multiple recurrences or the involvement of the regional nodes that makes the physician suspect the true significance of the previous symptoms. If the primary trouble occurs in the lymph-nodes the picture is still more confusing, and many times the axillary or inguinal swellings are incised because they are mistaken for abscesses. It is only occasionally that a patient in apparently good physical condition presents himself with generalized metastasis but is worried about the numerous little lumps over the body. Not infrequently there is a latent period between the appearance of the primary lesion and the metastasis. This latent period may be so long as to deceive the patient as to the real relation between the two, and it is only after close questioning that the physician discovers the primary cause, which the patient is only too prone to forget, or considers too trivial to mention.

The latent period may be as long as five or six years; in some instances the history dated back even longer, but this was open to doubt. The following is an example of a case in which there was a latent period of about three years and a rather rapid dissemination in about nine months. A married woman, aged forty-six, came to the Mayo Clinic in 1924 with definite symptoms of mild hyperthyroidism from adenomatous goitre. A thorough general examination did not disclose anything besides the adenomatous goitre and the usual features of hyperthyroidism. Following double resection of the goitre the pathologist's report corroborated the clinical diagnosis of hyperthyroidism. At that time there were no enlarged lymph-nodes, and the pelvic examinations were negative. In February, 1925, nine months later, the patient returned to the clinic complaining of many small lumps over the body of about nine months' duration. She said she had never felt so well in her life; the hyperthyroid symptoms had apparently completely disappeared. On general examination, the skin over the chest and back was peppered with hard firm nodules of various sizes. The right inguinal nodes were markedly enlarged and slightly tender. The pelvic examination disclosed two large immovable masses of firm consistence. After close questioning about the removal of moles and warts, the patient recollected that a small mole had been removed surgically from the anterior surface of the right leg, more than three years before. A healed scar without any sign of local recurrence was found over the anterior surface of the tibia. Pathologic examination of a nodule removed for diagnosis showed nonmelanotic melano-epithelioma. The patient died in November, 1925.

Thirty-five of the forty-nine patients in this series had been operated on or treated by some method for the purpose of removing the growth, previous to their coming to the clinic. The average duration of the lesion was approximately one year and four months. In twenty-two of the cases the lesion was either ulcerating or fungating and in some sinuses at the site of the lesion were discharging. Occasionally the lesion was described as bluish or, at times, brownish. Tenderness, inflammation and pain were not out-

standing features, and were only present, apparently, as a sequel to infection following ill-advised treatment.

In forty-nine cases, twenty-seven (55.1 per cent.) showed regional lymph-node metastasis, while seven (14.3 per cent.) showed generalized metastasis. In four there was only local recurrence.

Diagnosis.—The absolute diagnosis of nonmelanotic melano-epithelioma

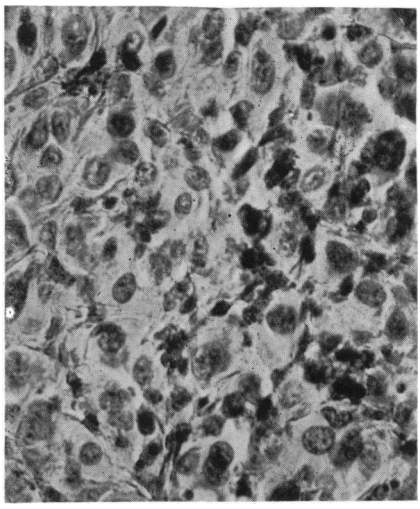

FIG. 8.—Melano-epithelioma showing melanin and alveolar arrangement of cells. Compare to Figure 4 (x200).

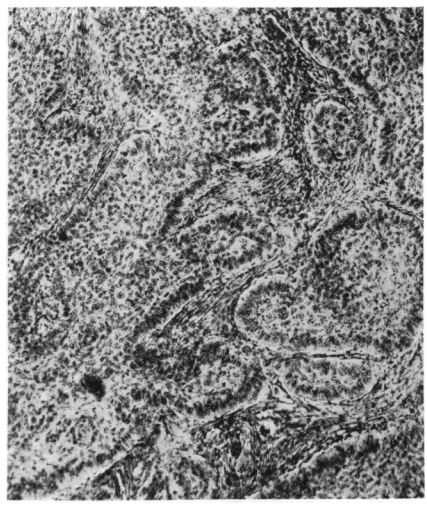

FIG. 9.—Squamous cell epithelioma of lower lip graded 4. A matrix and finger-like processes with the columnar cell formation in the advancing portions.

is only possible after microscopic examination. However, in a case of rapidly-growing tumor in which there was a history of a mole, usually on the lower extremities, and especially on the foot, which has been interfered with, or has been subjected to ill-advised treatment, the possibility of a melanotic epithelioma should be considered. If the tumor is very rapid in growth, and possibly if it is ulcerated or fungating in character, is prone to local recurrence or shows early regional lymph-node involvement, it is probably of the nonmelanotic variety.

The microscopic diagnosis of nonmelanotic melano-epithelioma is not simple. The cells may assume so many different forms and the mode of growth may be so varied as to tax the ability of the most competent pathologist. It is not at all unusual for nonmelanotic tumors to be diagnosed as small or large round-cell sarcoma, spindle-cell sarcoma, fibrosarcoma, myxomatous carcinoma or endothelioma. (Figs. 8 and 9.) Still the very fact that the cells are of such diverse shape and form, the mode of growth so varied, the individual cells so completely undifferentiated, and mitosis so frequently encountered, should be sufficient to remind one of the possibility of a nonmelanotic growth. If this diversified picture is found in adjacent areas of the same section, and especially if some definite connection is found with the epidermis, the diagnosis should be quite clear. Occasionally such a tumor may be pigmented due

to the extravasation of blood into the tumor and thus be mistaken for melanotic tumor. But the blood pigment usually has a brighter sheen, is distributed in clumps and irregular patches, and lacks the fine diffuse and regular distribution of melanin pigment.

Prognosis.—The prognosis at the very best is poor. All the tumors of the nonmelanotic variety in our series were graded 4 or 4+, according to Broders' classification. This would mean a good result in only 10 per cent. of the cases. But since in the recent revision of the term, grade 4 malignancy, Broders [4] has stated that it should signify from 75 to 100 per cent. undifferentiated cells and 0 per cent. to 25 per cent. differentiated cells, and since the nonmelanotic tumors are usually almost 100 per cent. undifferentiated, it is only reasonable to expect the results to be very unfavorable.

Forty-four of the forty-nine patients were traced. Thirty-nine (88.6 per cent.) were dead. Most of the patients not traced are no doubt dead because in several generalized metastasis was present when they were last examined. (Tabulation.)

TABULATION

RESULTS OF TREATMENT OF NONMELANOTIC MELANO-EPITHELIOMA

	Cases		Deaths		Patients living	Average post-operative therapeutic life (approximately)†	Range of post-operative therapeutic life (approximately)
	Total	Traced	Number	Per cent.			
Surgery only...	14	11	10	90.9	1 (7 months later)	18.8 months	2 weeks to 6.5 years
Radium or Röntgen-rays only*	5	5	4	80.0	1 (7 months later)	16.8 months	7 to 25 months
Surgery and radium or Röntgen-rays	9	8	5	62.5	3 (2 years 11 months 3 years 8 months 5 years 9 months)	6.1 months	4.5 to 9 months

* Excluding diagnostic biopsy.

† Date of death was not given in three cases in which surgery only was employed and in one in which there was surgery and radium or Röntgen-rays.

Treatment.—With the foregoing prognosis the treatment is far from satisfactory. The use of radium and Röntgen-rays is condemned by some and advocated by others. Wood advises against it in those cases amenable to surgery and Hertzler believes that radium and Röntgen-rays are absolutely contraindicated and worse than useless. Hutchins argues for the removal of moles by electrolysis, caustics or "high potential" treatments because of the good cosmetic result, lack of bleeding and less danger of infection. Owen, and Montgomery and Culver describe a case of melanotic tumor successfully treated by radium.

Thibaudeau and Schreiner report clinical cure in 50 per cent. of melanotic tumors before metastasis appeared and in half of these (25 per cent.) a clinical cure was obtained for two and a half years or more. One case in which the patient was still well after seven years was reported. In another inoperable case in which the tumor was situated at the inner canthus of the eye, the patient was reported to be well after two and a half years following filtered high-voltage Röntgen-ray treatment.

Coley and Hoguet, in their study of ninety-one cases of melanotic tumor, used Coley's serum (mixed toxins of erysipelas and *Bacillus prodigiosus*) with marked retardation of growth of the tumor.

In my series, radium or Röntgen-ray treatment was advised in inoperable cases and many were also advised to use Coley's serum, but lately the serum has not been urged. Operation, in the form of wide excision by cautery, amputation (if on a limb) with removal of the regional lymph-nodes, or irradiation of the regional lymphatics, was resorted to in cases amenable to treatment.

Desjardins [12] believes that the melanotic tumors are the most resistant variety of neoplasms but that occasionally certain cases do respond to radiotherapy. But in order to obtain any such response he maintains that treatment must be thorough. In some cases he has obtained encouraging and sometimes quite satisfactory results.

If a more favorable outlook is to be established stress must be placed on treatment which is anticipatory rather than remedial. "Cosmeticians" and beauty parlor "experts" have learned to give moles a wide berth. The mole has acquired the pseudonym of "touch-me-not" spot, from those who have had bitter experience with it. However, a mole which is constantly irritated, especially one on the lower extremities, and more especially one on the foot, should be removed by a wide excision, preferably by cautery, including the deep fascia and subcutaneous tissue. Any mole which is degenerating or showing evidence of beginning activity, such as bluish discoloration, or gradual increase in size, should be accorded the same treatment. And if unfortunately the mole shows beginning malignancy, then excision alone is not sufficient. The only safe treatment is complete removal of the regional lymph-nodes, as would be done in the case of a small nodule of carcinoma in the breast. New and Hansel do not believe that "removal of the glands of the neck in an attempt to block the growth from metastasizing is of value; nor is a block dissection of value when a gland of the neck is involved."

CONCLUSIONS

1. The nonmelanotic tumors belong to the same family as the melano-epitheliomas and differ only in the absence of pigment.

2. The absence of pigment in these tumors is evidence of their rapid growth, for melanin production is a form of differentiation.

3. Histologically it can be demonstrated that malignant changes begin in the basal-cell layer of the rete malpighii.

4. The arrangement and form of the individual cells are quite varied, and are evidence of a different stage of "dedifferentiation."

5. According to Broders' classification all of the forty-nine cases of non-melanotic melano-epithelioma occurring in the Mayo Clinic are of the grade 4 type.

6. A clinical review of these cases shows that they usually occur when the patient is past middle life. More than half of the growths are on the lower

extremities, especially on the foot, and in more than a third there is a history of a mole, nevus or wart.

7. The prognosis, as would be expected from any malignant growth graded 4, is very poor.

8. Prophylactic excision of moles, especially those occurring on the lower extremities, and wide excision by cautery, with eradication of regional lymph-nodes in moles showing malignant change, is advocated. Radium and Röntgen-rays should be used as an adjunct to surgery and in those cases not amenable to surgery.

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